PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference	FOR FURTHER ACTION
see form PCT/ISA/220	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/000073	12.01.2004	10.01.2003

International Patent Classification (IPC) or both national classification and IPC
A61K35/76, A61P31/04

Applicant
HEALTH PROTECTION AGENCY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Pilling, S

Telephone No. +49 89 2399-8461

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/000073

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 42 to 50 with regard to industrial applicability

because:

☒ the said international application, or the said claims Nos. 42-50 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-4,6-8,11,14-16,20-40,43,44,46-48
	No:	Claims	1,5,9,10,12,13,17,18,19,41,42,45,49,50
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	1-41 (for Claims 42 to 50 see comments under Item III)
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/000073

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 42 to 50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no international preliminary examination will be made in respect of these claims in respect of industrial applicability (Article 34(4)(a)(i) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D7 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

3. The relevant disclosure of each of these documents is summarised as follows;

D1: discloses that bacteriophages have enzymes that degrade exopolysaccharide (EPS) in bacterial biofilms.

D2: discloses that most bacteriophages have polysaccharide degrading enzymes including polysaccharide lyases.

D3: discloses that *Staphylococcus epidermidis* biofilm infections in CSF shunts can be treated with bacteriophage.

D4: discloses that *Escherichia coli* biofilm infections in Robbins devices can be treated with bacteriophage.

D5: discloses that *Pseudomona auruginosa* infections of skin grafts can be treated with bacteriophage.

D6: discloses that bacteriophage migration through *Pseudomona auruginosa* biofilms may be dependent on enzymatic degradation of alginate.

US'825

D7: discloses treatment of *Pseudomona auruginosa* infections associated with cystic fibrosis using alginate lyase. ✓✓

Claims 1 to 12, 28 to 30; compositions for treating a bacterial biofilm

4. Claim 1 defines "*A composition for treating a bacterial biofilm comprising a first bacteriophage..//..and a first polysaccharide lyase enzyme..Etc*". According to Claim 5 it appears that said polysaccharide lyase (PL) enzyme may simply be encoded by the bacteriophage of Claim 1. Thus, Claim 1 appears to define a composition comprising a bacteriophage encoding a PL enzyme, *i.e.* a bacteriophage *per se*. The present description appears to indicate that bacteriophages comprising PLs are known (see, for example present page 13 line 30 to page 14 line 2 and page 15 lines 21 to 28). Documents D1 and D2 further teach that bacteriophages inherently encode PL. Thus, it must be concluded that bacteriophage(s) encoding PL enzymes as defined in present Claim 1 are not new *per se* in view of these prior disclosures.

5. Thus, the subject matter of Claims 1, 5, 9, 10 and 12 is not new (Article 33(2) PCT).

6. The further features of Claims 2 to 4, 6 to 8, 11 and Claims 28 to 30 appear to be routine modifications that would occur to one of skill in this art. Thus, the subject matter of these claims lacks inventive step (Article 33(3) PCT).

Claims 13 to 22, 31 to 35; uses of a composition for the manufacture of a medicament

7. Each of documents D3 to D6 describes the use of bacteriophages to treat biofilms. As indicated above (see "compositions") it appears that bacteriophages inherently comprise PLs. Thus, although documents D3 to D6 do not explicitly refer to PLs, it appears highly likely that the bacteriophages disclosed in these documents would have encoded PL.

8. Thus, the subject matter of Claim 13, 17, 18 and 19 is not new in view of the disclosures of each of documents D3 to D6 (Article 33(2) PCT).

9. The further features of Claims 14 to 16, 20 to 22 and Claims 31 to 35 are routine

modifications that would occur to one of skill in this art. Thus, the subject matter of these claims lacks an inventive step in view of the disclosures of each of documents D3 to D6 (Article 33(2) PCT).

Claims 23 to 27: bacteriophages comprising a heterologous gene

10. None of the presently available prior art documents disclose a bacteriophage comprising a heterologous gene encoding a PL enzyme. Thus, the subject matter of Claim 23 is new (Article 33(2) PCT).

11. The closest prior art document appears to be document D1 since this document discloses that bacteriophages have enzymes that degrade exopolysaccharide (EPS) in bacterial biofilms. The difference between the bacteriophages of document D1 and those of present Claim 23 is that the presently claimed bacteriophages have "*a heterologous gene encoding a first polysaccharide lyase enzyme*". On the basis of the present description it appears that the introduction of a heterologous gene encoding a PL enables the bacteriophage to degrade bacterial EPS present in biofilms (see page 14 lines 15 to 18) such as those resulting from opportunistic bacterial infections (see page 14 lines 28 to 31).

12. Since document D1 already teaches that the susceptibility of bacterial biofilms to attack is at least partially dependent on polysaccharide degrading enzymes encoded by the bacteriophage, it does not appear inventive to modify a bacteriophage by introducing a heterologous gene encoding a particular polysaccharide degrading enzyme, *i.e.* a PL. The technical effects of this modification, *i.e.* enabling degradation of EPS present in bacterial biofilms, would have been wholly predictable on the basis of the teaching of document D1.

13. The further features of Claims 24 to 27 are either disclosed in document D1 or are routine modifications that would occur to one of skill in this art.

14. Thus the subject matter of Claim 23 to 27 is not inventive in view of the disclosure of document D1 (Article 33(3) PCT).

Claims 36 to 40: methods of making a modified bacteriophage

15. Similar considerations apply in respect of novelty and lack of inventive step of Claims 36 to 40 as previously set out herein above in respect of Claim 23. Thus the subject matter of Claims 36 to 40 is new (Article 33(2) PCT) but lacks an inventive step in view of the disclosure of D1 (Article 33(3) PCT).

Claim 41; methods of identifying a bacteriophage

16. Claim 41 is directed towards a method of identifying a bacteriophage comprising two steps "*a) identifying a bacteriophage that is capable of infecting a bacterial species or strain*" and "*b) confirming that said bacteriophage encodes a polysaccharide lyase..Etc*". Thus, Claim 41 appears to merely amount to a method of determining whether a bacteriophage encodes a PL. As noted above, it is clearly known that bacteriophages may produce PL (see the comments herein above in respect of Claim 1). Thus, the method of Claim 41 cannot be new (Article 33(2) PCT).

Claims 42 to 50; methods of treating a biofilm infection

17. Similar considerations apply in respect of lack of novelty and inventive step of Claims 42 to 50 as previously set out herein above in respect of Claim 13 to 22. Thus, the subject matter of Claims 42, 45, 49 and 50 is not new in view of the disclosures of documents D3 to D6 (Article 33(2) PCT). The subject matter of Claims 43, 44, 46 to 48 lacks an inventive step at least in view of the disclosures of these documents (Article 33(3) PCT).